Correlation Chart for Selected ICE Inhibitors In vitro and In vivo

1	2	3	4	5	6	7	8
Compound	Ki (nM) UV-visible	Cell PBMC IC50 (nM)	Whole human blood IC50 (nM)	PO % Inhib. (50 mg/kg)	IP % Inhib. (50 mg/kg)	Clearance Mouse, i.v. ml/min/kg	Clearance Rat, i.v. ml/min/kg
214e	7.5	1600	1500	75	78	23	12
265	47	4300		27	30	23	10-15
416	12	1200	3400	52	39		
434	4.9	1600	1800	80	74		
438	28	1000	700	13	40		
442	3.2	900	2000	10	0		
304a	200	14,000	2400		68		
302	4500	>20,000	>20,000		21		

1) Compounds that are ICE inhibitors in vitro inhibit IL-1ß production in vivo (decrease IL-1ß serum levels).

2) Relative inhibitory effects of ICE inhibitors (in vitro compared to in vivo) will depend on several factors, including in vivo clearance rates.

3) For compounds 214e and 265, lower in vitro inhibition constants (K_i(nM)) correlate with greater in vivo inhibitory activity when the in vivo clearance rates are similar.

How To Generate the Pharmacophore

1. Determine the "site points" where molecular subunits (i.e., H-bond donating, H-bond accepting, hydrophobic etc.) favorably bind to ICE

MCSS, GRID

2. Run de novo programs on simple ligand molecules comprising molecular subunits which can be used to form composite molecules

LUDI, LEAPFROG

3. Run docking programs to evaluate the ability to place simple ligand molecules into the active site

DOCK, AUTODOCK

4. Visually inspect the site points and simple molecules determined in steps 1-3, in the active site of ICE.

Quanta, Sybyl

5. Evaluate the electrostatic and hydrogen bonding potentials between the active site of ICE and the site points and simple fragments determined in steps 1-3.

Quanta, DELPHI, GRASP

6. Perform molecular dynamics (MD) to ensure that the simple fragments bind to the active site in a structurally and energentically favorable manner

AMBER, CHARMM